CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Dinotefuran

Chemical Code # 5822, **Tolerance #** 52911
SB 950 # NA

1/9/03

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Study not required at this time.

Toxicology one-liners are attached.

All record numbers through 187291 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: 030109
Thomas Moore, 1/9/03

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

** 143; 187282; "104-Week Dietary Chronic Toxicity and Carcinogenicity Study with MTI-446 in Rats"; (M.S. Weiler; Covance Laboratories Inc., Madison, WI; Study ID Covance 6648-131; 4/5/00); Ninety Crl:CD (SD)BR VAF/Plus rats/sex/group were fed in the diet 0, 60, 200, 2000 or 20000 ppm of MTI-446 (lot no. 22-00210, purity: 93.0%) for up to 104 weeks ((M) 0, 2.98, 9.89, 99.7, 991 mg/kg/day, (F) 0, 3.81, 12.5, 127, 1332 mg/kg/day). An additional ten animals/sex/group in the control and 20000 ppm groups were dosed for 26 weeks and then maintained for an additional recovery period of 6 weeks. There was no treatment-related effect upon survivability over the course of the study. The mean body weights and food consumption of the 20000 ppm males and females were lower than those of the controls over the course of the study ($p<0.05$). The mean weights of the 20000 ppm males were 93, 91, 93 and 96% of the controls at 26, 50, 78 and 105 weeks. For the 20000 ppm females, the mean weights were 91, 84, 78 and 75% of the controls at the same time intervals. No treatment-related effect upon hematology, clinical chemistry, ophthalmology or urinalysis was noted.. No treatment-related effect upon organ weights was apparent. In the histological examination, the males in the 20000 ppm treatment group exhibited an increased incidence of pelvic mineralization in the kidney (0: 5/100 vs. 20000: 27/100) and ulceration of the pelvis in the kidney (0: 0/100 vs. 20000: 5/100). For the females, there was a dose-related increase in the incidence of pulmonary carcinoma (0: 0/100, 60: 1/90, 200: 1/90, 2000: 2/90, 20000: 6/100). However, each of the tumors in the 20000 ppm treatment group was not primary, having arisen from another tissue. The increased incidence of pulmonary carcinoma was therefore not considered to be an adverse effect. **No adverse effect indicated. Chronic NOEL:** (M/F) 2000 ppm ((M) 99.7 mg/kg/day, (F) 127 mg/kg/day) (based upon lower mean body weight and food consumption for both the males and females of the 20000 ppm group and increased incidence of kidney lesions in the 20000 ppm males); **No oncogenicity indicated. Study acceptable.** (Moore, 9/11/02)

CHRONIC TOXICITY, RAT

See Combined rat above.

CHRONIC TOXICITY, DOG

** 141; 187280; "52-Week Dietary Chronic Toxicity Study with MTI-446 in Dogs"; (M.S. Weiler; Covance Laboratories Inc., Madison, WI; Study ID Covance 6648-129; 12/10/99); Four beagle dogs/sex/group received doses of 0, 640, 3200 or 16000 ppm of MTI-446 (lot no. 2200210, purity: 93.0%) in the diet for 52 weeks ((M): 0, 20.1, 111, 559 mg/kg/day, (F): 0, 22.3, 108, 512 mg/kg/day). No deaths resulted from the treatment. The mean body weight gain for the 16000 ppm males and the 3200 and 16000 ppm females was less than that of the controls. There was no treatment-related effect upon food consumption, ophthalmology, hematology, clinical chemistry or urinalysis. No treatment-related lesions were noted in the necropsy or histopathological examinations. **No adverse effect indicated. Chronic NOEL:** (M) 3200 ppm (111 mg/kg/day) (F) 640 ppm (22.3 mg/kg/day) (based upon reduced body weight gain for the 16000 ppm males and the 3200 ppm females). **Study acceptable.** (Moore, 9/4/02)

ONCOGENICITY, RAT

See Combined rat above.

ONCOGENICITY, MOUSE

** 142; 187281; "78-Week Dietary Carcinogenicity Study with MTI-446 in Mice"; (M.S. Weiler; Covance Laboratories Inc., Madison, WI; Study ID Covance 6648-130; 1/25/00); Seventy Crl:CD-1(ICR)BR VAF/Plus mice/sex/group received 0, 25, 250, 2500, or 25000 ppm of MTI-446 (lot no. 2200210, purity: 93.0%) in the diet for up to 78 weeks ((M): 0, 3.35, 34.1, 345.4, 3694 mg/kg/day, (F) 0, 4.38, 45.1, 441.2, 4728 mg/kg/day). There was no treatment-related effect upon survival. The mean weight gains for both sexes of the 25000 ppm group were less than that of the control

($p<0.05$). The mean body weights of the 25000 ppm animals were reduced by 4.7 and 9.1% for the males and females, respectively, as compared to the controls at the conclusion of the study. There was no treatment-related effect upon food consumption or hematology. There was no treatment-related effect upon absolute and relative organ weights. No treatment-related non-neoplastic lesions noted in the histopathological examination. There was an increased incidence of leiomyoma and leiomyosarcoma combined for the 25000 ppm treatment females which was not statistically significant (0: 2/70 vs. 25000: 5/70, $p=0.186$). No treatment-related neoplastic lesions were noted for the males. **No adverse effect indicated. Chronic NOEL:** (M/F) 2500 ppm ((M) 345.4 mg/kg/day, (F) 441.2 mg/kg/day) (based upon reduced body weight gain for the 25000 ppm treatment group); **Oncogenicity not evident. Study acceptable.** (Moore, 9/6/02)

REPRODUCTION, RAT

** 137; 187276; "MTI-446: Two Generation Reproduction Study in the Han Wistar Rat by Oral (dietary) Administration"; (H. Becker; RCC Ltd, Toxicology Division and Environmental Chemistry & Pharmanalytics Division, CH-4452 Itingen, Switzerland; Study No. 775192; 2/20/02); Twenty five HanIbm:WIST (SPF) rats/sex/group were treated in the diet with 0, 300, 1000, 3000 or 10000 ppm of MTI-446 (batch no. 5400810, purity: 98.9%) for two generations. The treatment included 10 weeks prior to mating, mating, 3 weeks of gestation and 3 weeks of lactation of the P generation. At that time, 45 F1 animals/sex/group were selected, 25 animals/sex/group as parents which were treated for a minimum of 10 weeks prior to mating, followed by mating and 3 weeks each of gestation and lactation of the F2 generation. The additional 20 animals/sex/group were examined at 6 weeks old using a modified Irwin screen functional test battery. The P and F1 males and P and F1 females in the 10000 ppm treatment group had a lower mean body weight than those of the controls at the end of the premating period (males, $p<0.05$, $p<0.01$) or during the gestation and/or lactation periods (females, $p<0.01$). There was no consistent treatment-related effect upon food consumption. No treatment-related effects were noted in the histopathological evaluation. There were no treatment-related effects upon the fertility or gestation indices. The mean litter sizes were not affected by the treatment. There was no treatment-related effect upon pup viability.

Mean pup weights for the 10000 ppm group of both generations were lower than those of the control on days 14 and 21 of the lactation period ($p<0.05$, $p<0.01$). The mean grip strength, forelimb for the males and hindlimb for the females, was lower than that of the controls at 6 weeks of age ($p<0.05$), possibly a function of lower body weights. Sperm analysis indicated reduced motility for the 10000 ppm F1 males ($p<0.01$), altered morphology for both the P and F1 10000 ppm males ($p<0.05$, $p<0.01$) and a reduced count for the 10000 ppm P males ($p<0.01$). These effects were not consistent between generations and did not result in diminished reproduction for the 10000 ppm treatment group. **No adverse effect indicated. Parental NOEL:** (M/F) 3000 ppm (M: 241.0 to 269.0 mg/kg/day, F: 211.9 to 477.7 mg/kg/day) (based upon reduced mean body weight and effect on grip strength of the 10000 ppm treatment group), **Reproduction NOEL:** 10000 ppm (M:822.1 to 934.7 mg/kg/day, F: 725.2 to 1653.9 mg/kg/day) (based upon the lack of a treatment-related effect at the highest dose tested), **Developmental NOEL:** 3000 ppm (M: 241.0 to 269.0 mg/kg/day, F: 211.9 to 477.7 mg/kg/day) (based upon lower mean pup weights in the 10000 ppm group of both generations); **Study acceptable.** (Moore, 8/29/02)

138; 187277; "MTI-446 Technical: Preliminary Two Generation Study in the Han Wistar Rat"; (J.A. Edwards, C. Knuppe and K.A. Weber; RCC Ltd, Toxicology Division and Environmental Chemistry & Pharmanalytics Division, CH-4452 Itingen, Switzerland; Study No. 774990; 8/8/01); Six HanIbm:WIST (SPF) rats/sex/group were treated in the diet with 0, 10000 or 20000 ppm of MTI-446 (batch no. 5400810, purity: 98.9%) for one generation ((M) 0, 700, 1340 mg/kg/day, (F) 0, 749 to 2145, 1507 to 3192 mg/kg/day). The treatment included 2 weeks prior to mating, mating, 3 weeks of gestation and 3 weeks of lactation of the P generation. Selected F1 offspring were maintained on the diet for an additional 2 weeks after weaning. No deaths resulted from the treatment. The mean body weights of both sexes in both treatment groups were less than those of the controls ($p<0.05$, $p<0.01$). Mean food consumption for both groups was less than that of the control at various time points ($p<0.05$). There was no treatment-related effect upon the fertility or gestation indices. There was an increased post-implanation loss for the 20000 ppm group ($p<0.01$) with an accompanying loss in litter size. Mean pup weight was less for both treatment

groups at 14 and 21 days post-partum ($p<0.05$, $p<0.01$). **No adverse effect indicated.** NOEL not established. **Study supplemental** (non-guideline study). (Moore, 8/30/02)

TERATOLOGY, RAT

** 133; 187272; "Teratogenicity Study of MTI-446 Given Orally to Rats"; (Takayuki Sakurai; Nippon Experimental Medical Research Institute Co., Ltd, Agatsuma-gun, Gunma, Japan; Project ID. H-97163; 6/8/98); Twenty four mated Crj: CD (SD) IGS female rats/group were dosed by oral gavage with 0, 100, 300 or 1000 mg/kg/day of MTI-446 (lot no. 2200210, purity: 92.9%) from day 6 through day 15 of gestation. No deaths resulted from the treatment. Mean body weight gain for the 1000 mg/kg dams was less than that of the controls for the treatment period between 6 and 11 days ($p<0.05$). Mean food consumption for the high dose dams was likewise reduced during this period ($p<0.05$). There were no treatment-related effects upon the development of the fetuses. **No adverse effect indicated. Maternal NOEL:** 300 mg/kg/day (based upon reduced mean body weight gain and food consumption for the 1000 mg/kg dams);
Developmental NOEL: 1000 mg/kg/day (based upon the no treatment-related effects noted at the highest dose tested); **Study acceptable.** (Moore, 8/23/02)

132; 187271; "A Dose-Finding Teratogenicity Study of MTI-446 Given Orally to Rats"; (Takayuki Sakurai; Nippon Experimental Medical Research Institute Co., Ltd, Agatsuma-gun, Gunma, Japan; Project ID H-97162; 1/16/98); Six mated Crj: CD (SD) IGS female rats/group were dosed by oral gavage with 0, 30, 100, 300 or 1000 mg/kg/day of MTI-446 (lot no. 2200210, purity: 92.9%) from day 6 through day 15 of gestation. All of the dams survived the treatment. The mean body weight gain of the 1000 mg/kg females was lower than that of the control on the first 2 days of dosing, recovering thereafter. Mean food consumption although lower for the high dose dams than the controls was not significantly affected. No clinical signs of toxicity were noted. There were no apparent treatment-related effects upon post-implantation loss, incidence of external abnormalities, and mean fetal weights. **No adverse effect indicated. Study supplemental** (non-guideline study). (Moore, 8/23/02)

TERATOLOGY, RABBIT

** 135; 187274; "Teratogenicity Study of MTI-446 Given Orally to Rabbits"; (Takayuki Sakurai; Nippon Experimental Medical Research Institute Co., Ltd, Agatsuma-gun, Gunma, Japan; Project ID H-97166; 12/3/98); Twenty two mated New Zealand female rabbits/group were dosed by oral gavage with 0, 52, 125 or 300 mg/kg/day of MTI-446 (lot no. 2200210, purity: 92.9%) from day 6 to day 18 of gestation. One control doe died on day 6 due to a dosing accident. One 300 mg/kg female was euthanized on day 7 because of ill health. Treatment-related clinical signs of panting, resting in the prone position, hypoactivity, reddening of the ears and nose and tremors were noted only for the 300 mg/kg females, clearing by day 14 in all animals. Mean body weight gain and food consumption was reduced for the 300 mg/kg females ($p<0.05$, 0.01). Necropsy results revealed the incidence of gray white plaques in the stomach of the 125 and 300 mg/kg treatment group (0: 0/22 vs. 125: 15/22 and 300: 18/22). There was an increased incidence in the number of late fetal deaths for the 125 and 300 mg/kg groups (0: 1/158 vs. 125: 4/182 and 300: 6/159). However, the increase per litter was not statistically significant and the number of live fetuses per litter was not affected. **No adverse effect indicated. Maternal NOEL:** 52 mg/kg/day (based upon the incidence of stomach lesions noted for the 125 mg/kg treatment group); **Developmental NOEL:** 300 mg/kg/day (no effect at the highest dose tested); **Study acceptable.** (Moore, 8/27/02)

134; 187273; "A Dose-Finding Teratogenicity Study of MTI-446 Given Orally to Rabbits"; (Takayuki Sakurai; Nippon Experimental Medical Research Institute Co., Ltd, Agatsuma-gun, Gunma, Japan; Project ID H-97165; 6/8/98); Six mated New Zealand female rabbits/group were dosed by oral gavage with 0, 100, 300 or 1000 mg/kg/day of MTI-446 (lot no. 2200210, purity: 92.9%) in 0.5% CMC-Na aqueous solution from day 6 to day 18 of gestation. No deaths resulted from the treatment. Both 300 and 1000 mg/kg treatment group does exhibited treatment-related effects of tremors, decreased activity, and panting. The signs were more severe for the does in the 1000 mg/kg group. Body weight gain and food consumption was reduced for the 1000 mg/kg females. Four does in the 1000 mg/kg group and one control female aborted. The mean body

weight of the 1000 mg/kg fetuses was less than that of the control. Otherwise, no other effects on the fetuses were evident. **No adverse effect indicated. NOEL** was not determined as this study was only for dose-range finding. **Study supplemental**. (Moore, 8/26/02)

136; 187275; "A Single and 2-Week Repeated Dose Preliminary Study of MTI-446 Given Orally to Rabbits"; (Takayuki Sakurai; Nippon Experimental Medical Research Institute Co., Ltd, Agatsuma-gun, Gunma, Japan; Project ID H-97164; 1/16/98); Two studies were performed in which mated New Zealand White female rabbits were dosed by oral gavage with MTI-446 (lot no. 2200210, purity: 92.9%). In the first study, 2 animals/group were treated with a single dose of 100, 300, 1000 or 2000 mg/kg of the test material and observed for 5 days. None of the animals died. For the animals treated with 300 mg/kg and above, clinical signs included hypoactivity, tremors and flushing of the ears and nose. At 1000 and 2000 mg/kg, the animals lay in the prone position. At 2000 mg/kg, panting, sedation and ptosis were noted. Anorexia was evident for up to 3 days post-dose in that treatment group. In the necropsy examination, gray white plaques were noted in the stomach of the 1000 and 2000 mg/kg animals. In the 2nd study, 3 animals/group were dosed with 0, 100, 300 or 1000 mg/kg of the test material for 14 days. No deaths resulted from the treatment. Clinical signs for the 300 mg/kg treatment group and above were hypoactivity, panting, flushing of the ears and nose and sedation. The animals in the 1000 mg/kg group were also lying in the prone position. Signs were evident from the 1st day of treatment but lessened in severity as the treatment progressed. Body weight gain was reduced in the 1000 mg/kg group. Food consumption was likewise reduced for this group. In the necropsy examination, gray white plaques or dark red spots in the stomach and pale brown discoloration of the liver were noted for the 300 and 1000 mg/kg groups. One animal in the 100 mg/kg group had a dark brown discoloration of the liver and gray white plaques on the kidney. **No adverse effects indicated.** NOEL not determined. **Study supplemental** (non-guideline study). (Moore, 8/27/02)

GENE MUTATION

** 144; 187283; "MTI-446: Microbial Reverse Mutation Assay"; (Chieko Takeda and Motoi Ishidate; Chromosome Research Center (CRC), Orympus Optical Co., Ltd., Hachioji-Shi, Tokyo, Japan; Study No. CRC3113; 10/3/96); *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2-*uvr*A were preincubated for 20 minutes, followed by incubation for 48 hours at 37° C with MTI-446 (lot no. 22-00110, purity: 96.5%) at concentrations ranging from 1.2 to 5000 ug/plate in the 1st trial and from 313 to 5000 ug/plate in the 2nd trial with and without S9 activation. All doses of the test article, the vehicle controls and the positive controls were plated in triplicate. No treatment-related increase in revertant colonies was noted with or without activation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 9/12/02)

** 145; 187284; "MTI-446 Technical Material: Mutation at the Thymidine Kinase (tk) Locus of Mouse Lymphoma L5178Y Cells (MLA) using the Microtitre® Fluctuation Technique"; (M. Lloyd; Covance Laboratories Ltd, North Yorkshire HG3 1PY, England; Report No. 719/15-D6173; 2/8/02); Mouse lymphoma L5178Y cells ($TK^{+/-}$) were treated with MTI-446 (batch no. 5400610, purity: 99.1%) at concentrations ranging from 400 to 2022 ug/ml under condition of activation and non-activation for 3 hours of treatment in the 1st trial and for 3 hours (activation) or 24 hours (non-activation) of treatment in the 2nd trial at 37° C. The samples were further incubated to permit the expression of the 5-trifluorothymidine (TFT) resistant mutants. Each treatment was cultured in duplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the mutation frequency. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 9/13/02)

CHROMOSOME EFFECTS

146; 187285; "MTI-446: *In Vitro* Mammalian Cytogenetics Test"; (Takunori Satou and Motoi Ishidate; Chromosome Research Center (CRC), Orympus Optical Co., Ltd., Hachioji-Shi, Tokyo, Japan; Study No. CRC0076; 10/15/96); Chinese hamster lung (CHL/IU) cells were exposed to concentrations of MTI-446 (lot no. 22-00110; purity: 96.5%) ranging from 500 to 2000 _g/ml under conditions of non-activation and activation at 37° C. For the non-activated cultures, the cells were

exposed to the test material for 24 or 48 hours. In the activated samples, the cells were exposed for 6 hours, washed and incubated for an additional 18 hours. A phenobarbital and 5,6-benzoflavone-induced rat liver S9 fraction was used to metabolize the test material. No treatment-related increases in chromosomal aberrations were noted under conditions of either non-activation or activation. **No adverse effect indicated.** The positive controls were functional. However, inadequate documentation was provided that the cells were actually sampled during the 1st metaphase for aberrations. **Study unacceptable**, possibly upgradeable to acceptable with documentation that the cells were actually sampled during this time frame. (Moore, 9/24/02)

** 147; 187286; "Micronucleus Test of EXP-316 with Mice"; (Madoka Nakajima; Biosafety Research Center, Foods, Drugs & Pesticides, An-Pyo Center, Shizuoka 437-12, Japan; Study No. 2498; 3/15/95); Six BDF_1 (C57BL/6 x DBA/2) male mice/group were treated by oral gavage with 0, 270, 540 or 1080 mg/kg of EXP 316 (lot no. OFU-1207; purity: 99%+) once per day for two days. Animals were euthanized at 24 hours after the last dose. A positive control group of 6 animals were treated by intraperitoneal injection with mitomycin C, 2 mg/kg, and were euthanized 24 hours post-dose. Bone marrow samples from the femur were examined and the ratio of polychromatic (PCE) to the total number of erythrocytes and the percentage of PCE with a micronucleus were determined. No treatment-related increase in the number of PCEs with a micronucleus was noted. The positive control was functional. **No adverse effect indicated. Study acceptable.** (Moore, 9/24/02)

DNA DAMAGE

** 148; 187287; "A DNA Repair Assay of *Bacillus subtilis* on MTI-446"; (Yoshihiro Oguma; BML, INC., Division of Safety Evaluation, Saitama 350-1101, Japan; Study No. 4731; 10/2/96); *Bacillus subtilis* H17 (rec^+) and M45 (rec^-) strains were exposed to concentrations of MTI-446 (lot no. 22-00110, purity: 99.1%) ranging from 1000 to16000 ug/disk for 24 hours at 37° C under conditions of non-activation and activation in duplicate samples for a single trial. The S9 fraction used to metabolize the test material was derived from the livers of male Sprague-Dawley rats induced with phenobarbital and 5,6-benzoflavone. No zones of inhibition resulted from the treatment with the test material. **No adverse effect indicated.** Positive controls were functional. **Study acceptable.** (Moore, 9/24/02)

NEUROTOXICITY

52911-150; 187289; "Acute Oral Gavage Neurotoxicity Study of MTI-446 in Rats"; (M.S. Weiler; Covance Laboratories Inc., Madison, WI; Study ID Covance 6648-147; 8/6/01); Ten Crl:CD(SD) BR rats/sex/group were dosed orally by gavage with 0, 325, 750 or 1500 mg/kg of MTI-446 (lot no. 2200210, purity: 93.0%). No deaths resulted from the treatment. No statistically-significant treatment-related effects were noted in the FOB evaluations. However, in the open-field observations, 2 of the 10 1500 mg/kg males did demonstrate low locomotor activity in contrast to none of the control males. This observation conformed somewhat with the decreased motor activity which was measured for both sexes of the 1500 mg/kg group in the 0 to 10 minute interval ($p<0.05$) and for the total count for the females in this group ($p<0.05$). In addition, in the physiological measurements, the mean body temperatures of both sexes in the 1500 mg/kg group were less than those of the control on Day 1. These values, however, were not statistically significant. **No adverse effect indicated. ACUTE NOEL:** 750 mg/kg (based upon the lower motor activity noted for the 1500 mg/kg treatment group); **Study unacceptable**, possibly upgradeable with the submission of documentation for positive controls). (Moore, 8/12/02)

52911-149; 187288; "13-Week Dietary Neurotoxicity Study with MTI-446 in Rats"; (M.S. Weiler; Covance Laboratories Inc., Madison, WI; Study ID. Covance 6648-148; 9/18/01); Ten Crl:CD(SD) BR rats/sex/group were dosed in the diet with 0, 500, 5000 or 50000 ppm of MTI-446 (lot no. 22-00210, purity: 93.0%) for 13 weeks ((M) 0, 32.8, 327, 3413 mg/kg/day, (F) 0, 40.0, 400, 3806 mg/kg/day). No deaths resulted from the treatment. The mean body weights and body weight gain for both sexes of the 50000 ppm group were less than those of the control group ($p<0.05$). Reduced food consumption was noted for both sexes in the 50000 ppm group during the study ($p<0.05$). The mean body temperature of the 50000 ppm females at week 2 was less than that of

the control ($p<0.05$). No other FOB parameters were affected by the treatment. The mean motor activity of the 50000 ppm females was less than that of the controls on week 2 ($p<0.05$). No treatment-related lesions were noted in the histopathology examination. **No adverse effect indicated. Subchronic NOEL:** 5000 ppm (M: 327 mg/kg/day, F: 400 mg/kg/day) (based upon lower mean body weight, body weight gain and food consumption for both sexes in the 50000 ppm group and reduced mean motor activity and body temperature for the 50000 ppm females); **Study unacceptable**, possibly upgradeable with the submission of positive control test documentation. (Moore, 9/26/02)

SUPPLEMENTAL AND SUBCHRONIC STUDIES

52911-124; 187263; "4-Week Dietary Toxicity Study with MTI-446 in Rats"; (M.S. Weiler; Corning Hazleton Inc., Madison, WI; Project ID: CHW 6648-125; 12/15/97); Five Crl:CD (SD)BR VAF/Plus rats/sex/group were fed in the diet 0, 5000, 25000 or 50000 ppm of MTI-446 (lot no. 22-00110, purity: 96.5%) for 4 weeks ((M) 0, 390.2, 1814, 3720 mg/kg/day, (F) 0, 450.5, 2183, 4222 mg/kg/day). No deaths resulted from the treatment. Mean body weight gain was lower for the 25000 and 50000 ppm males and for the 50000 ppm females during the 1st week of the study and for the 50000 ppm males during the 2nd week ($p<0.05$). Mean food consumption was likewise lower for these animals at the same time points ($p<0.05$). There were no treatment-related effects upon the hematology or urinalysis. The mean serum glucose level was lower for the 50000 ppm males than that of the controls ($p<0.05$). The mean serum cholesterol levels were greater for the 25000 and 50000 ppm males ($p<0.05$). Although the mean absolute heart, spleen, liver, and kidney weights were lower for the 50000 ppm males ($p<0.05$), the mean relative weights for these organs were not affected by the treatment. Likewise, the mean absolute heart weight for the 50000 ppm females was lower than that of the controls ($p<0.05$), but the relative weight was not significantly different. There were no treatment-related lesions noted in the histopathological examination. **No adverse effect indicated. NOEL:** (M) 5000 ppm (390.2 mg/kg/day) (based upon reduced body weight gain noted for the 25000 ppm males), (F) 25000 ppm (2182 mg/kg/day) (based upon reduced body weight gain noted for the 50000 ppm females); **Study supplemental** (non-guideline study). (Moore, 8/13/02)

52911-125; 187624; "4-Week Dietary Toxicity Study with MTI-446 in Mice"; (M.S. Weiler; Corning Hazleton Inc., Madison, WI; Project ID CHW 6648-124; 12/15/97); Ten Crl:CD-1 (ICR)BR VAF/Plus mice/sex/group were treated in the diet with 0, 5000, 25000 or 50000 ppm of MTI-446 (lot no. 22-00110, purity: 96.5%) for 4 weeks. One male in the 50000 ppm group died on the 3rd day of the study for a non-treatment-related cause and was replaced. Mean body weight gain was lower for both sexes in the 25000 and 50000 ppm treatment groups ($p<0.05$). There were no treatment-related effects upon the hematology or clinical chemistry. In the necropsy examination, there were no effects upon the organ weights. No microscopic lesions were noted in the histopathology examination. **No adverse effects indicated. NOEL:** (M/F) 5000 ppm ((M): 901 mg/kg/day, (F) 1043 mg/kg/day) (based upon reduced body weight gain observed for both sexes in the 25000 ppm treatment group); **Study supplemental** (non-guideline study). (Moore, 8/14/02)

52911-129; 187268; "14-Day Range-Finding Dermal Toxicity Study with MTI-446 in Rats"; (S.M. Henwood; Covance Laboratories Inc., Madison, WI; Study ID Covance 6648-150; 7/2/01); The skin of 5 Crl:CD (SD) IGS BR rats/sex/group was exposed to 0, 40, 200 or 1000 mg/kg/day of MTI-446 (lot no. 2200210, purity: 93.0%) 6 hours/day for 14 days. The test material was suspended in 0.5% carboxymethyl cellulose and dosed at a volume of 2 ml/kg. No deaths or treatment-related signs were evident. No treatment-related effect upon mean body weight was evident. Atonia was noted for the skin of the 200 and 1000 mg/kg/day treatment group. **No adverse effect indicated. Systemic NOEL:** (M/F) > 1000 mg/kg/day (based upon the lack of treatment-related effects at the highest dose tested); **Dermal Irritation NOEL:** 40 mg/kg/day (based upon the incidence and severity of dermal irritation noted for the 200 mg/kg group); **Study acceptable.** (Moore, 8/21/02)

52911-131; 187270; " MTI-446: 28-Day Inhalation (nose-only)Toxicity Study in the Rat"; (N.M. Shepherd; Study No. 719/16; 2/26/02); Ten Crl:WI(GLx/BRL/Han)BR rats/sex/group were exposed to 0, 0.22, 0.66 or 2.08 mg/l (gravimetric) of MTI-446 (batch no. 5400610; purity: 99.1%) 6

hours/day for 29 or 30 days. The mean MMAD (GSD) values were (0.22) 2.03 (3.31) um, (0.66) 1.80 (3.60) um, (2.08) 2.04 (3.07) um (note values calculated by reviewer do not correspond with the values for the high exposure group). No deaths resulted from the exposures. In the 1st week, the mean body weight gains of the 3 exposure groups were less than that of the control group ($p<0.05$). However, the body weight gains were not affected for the remainder of the study. There were no treatment-related effects upon the hematology, clinical chemistry, ophthalmology and urinalysis. The mean organ weights were not affected by the treatment. No treatment-related lesions were evident in the histopathological examination. **No adverse effect indicated. NOEL:** (M/F) > 2.08 mg/l (based upon no treatment-related effects at the highest exposure tested); **Study supplemental** (non-guideline study)**.** (Moore, 8/22/02)

139; 187278; "Repeated Dose Toxicity Test of MTI-446 Mixed in the Diet for One Week Using Dogs"; (Isao Teramoto; Jitsuiken Medical Research Institute, Inc., Agatsuma-gun, Gunma, Japan; Project ID H-97327; 2/28/98); One beagle dog/sex/group was treated in the diet with 5000, 20000, 30000 or 40000 ppm of MTI-446 (lot no. 2200210, purity: 92.9%) for one week. Note that the animals receiving 30000 ppm and 40000 ppm in the diet, initially received1250 and 0 ppm, respectively, of the test material for a week preceding the treatment with the higher concentrations. Although food consumption was lower for the 30000 and 40000 ppm groups, there was no obvious effect upon the body weights of these animals. No obvious treatment-related effect was noted in the hematology, clinical chemistry, and urinalysis. The necropsy and histopathological examinations did not reveal any treatment-related lesions. **No adverse effect indicated.** No NOEL determined. **Study supplemental** (non-guideline study). (Moore, 9/3/02)

140; 187279; "Repeated Dose Toxicity Test of MTI-446 by Forced Oral Administration for One Week Using Dogs"; (Isao Teramoto; Jitsuiken Medical Research Institute, Inc., Agatsuma-gun, Gunma, Japan; Project ID H-97326; 2/28/98); One beagle dog/sex/group was treated by oral gavage with 0, 30, 100 or 300 mg/kg/day of MTI-446 (lot no. 2200210, purity: 92.9%) in capsules for one week. No deaths resulted from the treatment. Loose stools were noted intermittently for the 300 mg/kg animals. Diarrhea or vomiting was reported during the 1st 4 days of treatment for these animals. The 100 mg/kg animals also exhibited loose stools during the 1st 3 to 4 days of treatment. Otherwise, no other treatment-related signs were noted. No obvious treatment-related effect was noted in the hematology, clinical chemistry, and urinalysis. The necropsy and histopathological examinations did not reveal any treatment-related lesions. **No adverse effect indicated.** No NOEL determined. **Study supplemental** (non-guideline study). (Moore, 9/3/02)

52911-126; 187265; "13-Week Dietary Toxicity Study with MTI-446 in Rats"; (M.S. Weiler; Corning Hazleton Inc., Madison, WI; Project ID CHW 6648-127; 12/31/97); Ten Crl:CD (SD)BR VAF/Plus rats/sex/group were fed in the diet 0, 500, 5000, 25000 or 50000 ppm of MTI-446 (lot no. 22-00110, purity: 96.5%) for 13 weeks ((M) 0, 34, 336, 1623, 3156 mg/kg/day, (F) 0, 38, 384, 1871, 3616 mg/kg/day). No deaths occurred during the study. Mean body weight gain was lower for the 25000 and 50000 ppm males and for the 5000 ppm females and above ($p<0.05$). Food consumption was likewise lower for these groups as well as for the 500 ppm females at various times during the study ($p<0.05$). There was no treatment-related effect upon the hematology, urinalysis or ophthalmology. In the clinical chemistry examination, the mean glucose and total protein levels were lower than that of the control for the 50000 ppm males ($p<0.05$). The globulin level was lower for both the 25000 and 50000 ppm males and the urea nitrogen was increased for the 50000 ppm males ($p<0.05$). No effects were noted for the females. The absolute weights for the pituitary, kidneys, heart, thymus, and spleen for the either or both sexes in the 50000 ppm group ($p<0.05$) were less than those of the controls. However, the relative weights of these organs were not significantly affected by the treatment. The absolute liver weights were lower for both sexes in the 50000 ppm group ($p<0.05$). The relative weight of the males was not affected. For the females the relative liver weight was increased over that of the control. However, there were no apparent lesions in the liver which signified a possible treatment-related effect. The relative brain weights were increased for both sexes in the 50000 ppm group and for the females in the 25000 ppm group. Likewise, the relative testis and epididymis weights were increased for the 50000 ppm males. However, no lesions were noted in the histopathological examination. The

mean absolute adrenal weight was lower for the 50000 ppm females, but the relative weight was not affected by the treatment. In the histopathological examination, increased vacuolization of the zona glomerulosa of the adrenal cortex was noted for the 5000 ppm males and above and the 25000 and 50000 ppm females ((M) 0:0/10, 5000: 3/10, 25000: 2/10, 50000: 4/10, (F) 0:0/10, 25000: 6/10, 50000: 10/10). Increased vacuolization was also noted in the zona fasciculata of the adrenal cortex of the 5000 ppm males and above (0: 1/10, 5000: 2/10, 25000: 3/10, 50000: 5/10). **No adverse effect indicated. Subchronic NOEL:** (M/F) 500 ppm ((M): 34 mg/kg/day, (F): 38 mg/kg/day) (based upon lesions in the adrenal cortex of the males in the 5000 ppm treatment group and reduced body weight gain for the females in the 5000 ppm treatment group). **Study acceptable.** (Moore, 8/16/02)

52911-127; 187266; "13-Week Dietary Toxicity Study with MTI-446 in Mice"; (M.S. Weiler; Corning Hazleton Inc., Madison, WI; Project ID CHW 6648-126; 12/31/97); Ten Crl:CD-1 (ICR)BR VAF/Plus mice/sex/group were treated in the diet with 0, 500, 5000, 25000 or 50000 ppm of MTI-446 (lot no. 22-00110, purity: 96.5%) for 13 weeks ((M) 0, 81, 844, 4442, 10635 mg/kg/day, (F) 102, 1064, 5414, 11560 mg/kg/day). The mean body weight and body weight gain for the 50000 ppm treatment group were less than that of the control animals ($p<0.05$). No treatment-related effects were noted for the hematology, clinical chemistry and ophthalmology. The absolute kidney, liver and heart weights for the 50000 ppm females were less than those of the controls ($p<0.05$). However, the relative weights of these organs were not significantly affected. The relative mean brain weights of both sexes in the 50000 ppm treatment group were greater than those of the controls ($p<0.05$). No treatment-related lesions were noted in the histopathological examination. **No adverse effects indicated. Subchronic NOEL:** (M/F) 25000 ppm ((M): 4442 mg/kg/day, (F) 5414 mg/kg/day) (based upon reduced body weight gain for the 50000 ppm treatment group); **Study acceptable.** (Moore, 8/19/02)

52911-128; 187267; "13-Week Dietary Toxicity Study with MTI-446 in Dogs"; (M.S. Weiler; Covance Laboratories Inc., Madison, WI; Project ID Covance 6648-128; 5/13/99); Four beagle dogs/sex/group received doses of 0, 1600, 8000 or 24000 ppm of MTI-446 (lot no. 2200110, purity: 92.9%) in the diet for 13 weeks ((M): 0, 58.0, 307, 862 mg/kg/day, (F): 0, 58.0, 323, 950 mg/kg/day). No deaths resulted from the treatment. Initially, the high dose level was 40000 ppm, but was first reduced to 30000 ppm after 4 days and finally to 24000 ppm after 11 days due to the unpalatability of the test material. The mean body weight gain and food consumption were reduced for the high dose treatment group for the first week of the study. No apparent treatment-related effect was noted thereafter. There was no treatment-related effect upon the hematology, ophthalmology and urinalysis. In the clinical chemistry, the mean SGPT activity level for both sexes of the 24000 ppm group was reduced after 5 and 13 weeks of treatment ($p<0.05$). However, this effect is not considered to be a manifestation of toxicity. There was no treatment-related effect upon any organ weights. No treatment-related lesions evident in the histopathological examination. **No adverse effect evident. Subchronic NOEL:** (M/F) > 24000 ppm ((M) > 862 mg/kg/day, (F) > 950 mg/kg/day) (based upon the lack of treatment-related effects at the highest treatment level); **Study acceptable.** (Moore, 8/20/02)

52911-130; 187269; "28-Day Dermal Toxicity Study with MTI-446 in Rats"; (S.M. Henwood; Covance Laboratories Inc., Madison, WI; Study ID Covance 6648-149; 10/12/01); The skin of 10 Crl:CD (SD) IGS BR rats/sex/group was exposed to 0, 40, 200 or 1000 mg/kg/day of MTI-446 (lot no. 2200210, purity: 93.0%) 6 hours/day for 29 days. The test material was suspended in 0.5% carboxymethyl cellulose and dosed at a volume of 2 ml/kg. No deaths or treatment-related signs were evident. No treatment-related effect upon mean body weight was evident. Atonia was noted for the skin of the 2 females in the 1000 mg/kg/day treatment group. An increased incidence and severity of acanthosis was noted for the females in the 1000 mg/kg group. **No adverse effect indicated. Systemic NOEL:** (M/F) > 1000 mg/kg/day (based upon the lack of treatment-related effects at the highest dose tested); **Dermal Irritation NOEL:** 200 mg/kg/day (based upon the incidence and severity of dermal irritation noted for the 1000 mg/kg females); **Study acceptable.** (Moore, 8/21/02)

METABOLISM STUDIES

** 151; 187290; "Metabolism of [^{14}C] MTI-446 in Rats"; (T. Chang; Covance Laboratories Inc., Madison, WI; Project ID. Covance 6648-136; 1/27/00); Crl:CD(SD)BR rats of both sexes were dosed by oral gavage with either 50 (low dose) or 1000 mg/kg (high dose) of [^{14}C] MTI-446 ([F-^{14}C]-MTI-446, lot no. 5091-20, radiochemical purity: >98.0%, specific activity: 28.9 uCi/mg, lot no. 5109-34, radiochemical purity: 100%, specific activity: 27.5 uCi/mg; [G-^{14}C]-MTI-446, lot no. 5091-30, radiochemical purity: >98.0%, specific activity: 42.9 uCi/mg; lot no. 5109-28, radiochemical purity: 100%, specific activity: 39.2 uCi/mg and MTI-446, lot no. 22-00210; purity: 98.92%, lot no. OFU-1265, purity: 99.47%), using single dose and multiple dosing regimens up to 15 days (low dose only). In addition, one group received an iv injection of 50 mg/kg of the test material. Pregnant dams at 18 days of gestation were dosed orally with 50 mg/kg of the test material.. Lactating females at approximately 12 days after parturition were dosed orally with 50 mg/kg of the test material. Hla(SD)CVF rats of both sexes which had cannulated bile ducts were dosed with either 50 or 1000 mg/kg of the test material. Excretion profiles of the radiolabel were developed, using the various dosing regimens. Radiolabel was recovered from the plasma in order to derive the pharmacokinetic profile. Tissue distribution of the radiolabel was analyzed. The concentration of the radiolabel in the near-term fetus was compared with that in the dam. The concentration in the radiolabel in the milk of the lactating female was compared that in the blood and plasma. Whole-body autoradiography was used to localize the sites of radioactivity at various time points post-dose. Further analysis of the radiolabeled compounds was performed in order to characterize the metabolites. In a preliminary study, minimal radiolabel was recovered in the expired air as CO_2 or volatiles. A high percentage of the administered dose was recovered in the urine (87.7 to 99.8%, including both low and high doses and multiple dosing regimens) with 92 to 97% of that being the parent compound. Fecal excretion ranged from 1.06 to 3.16% of the administered dose. Very little of the radiolabel was recovered in the bile. The pharmacokinetic parameters ranged in the following manner: T1/2, 3.6 to 16.1 hours, Tmax, 0.25 to 0.625 hours for the low dose, 2.0 to 2.1 for the high dose, Cmax, 40.8 to 47.4 ppm for the low dose, 471 to 566 ppm for the high dose. The concentration of the radiolabel in the fetus was quite similar to that of the dam. The radiolabel concentration in the milk was slightly higher than that reflected in the plasma and blood. The radiolabel was well distributed throughout the body with the highest levels recovered from the stomach, and kidneys. The test material was very minimally metabolized despite having been absorbed through the hepatic portal system. **Study acceptable**. (Moore, 10/4/02)

152; 187291; "Absorption, Distribution, Metabolism, and Excretion of [G-^{14}C] MTI-446 in Following Administration of a Single Oral Dose to Neonatal Rats"; (T. Cheng and S. Howard; Covance Laboratories Inc., Madison, WI; Project ID. 6648-141; 1/28/00); Twenty-five Crl:CD(SD) BR 12-day old rat pups/sex were dosed by oral gavage with 50 mg/kg of [G-^{14}C] MTI-446 (lot no. VB9304, radiopurity: 99.6%, specific activity: 27 mCi/mmol; MTI-446, lot no. OFU-1265, chemical purity: 99.47%). Five pups/sex each were euthanized at 0.5 and 1.5 hours post-dose. The remaining 15 pups/sex were euthanized at 4 hours post-dose. An additional 3 pups/sex dosed in the same manner and one pup/sex/time point was euthanized at 0.5, 1.5 and 4 hours post-dose. These animals were examined by whole-body autoradiography technique. The profile of the radiolabel in the pups demonstrated a rapid uptake and tissue distribution within the first 4 hours post-dose. The radiolabel was well distributed throughout the body as demonstrated in the whole-body autoradiography. The highest concentration of radiolabel was in the stomach contents at 0.5 hours which had diminished by 4 hours with a correponding increase in excreta in that time frame. These results were similar to those observed in the adults with one appreciable difference. Uptake from the stomach by the adults was apparently even more rapid than that observed for the pups (male pup stomach contents at 0.5 hours was 52.2% as compared to that of the adults of 2.41%). **Study supplemental** (non-guideline study). (Moore, 10/7/02)